

SENATE APPROPRIATIONS COMMITTEES SIGNIFICANT ITEMS

SENATE COMMITTEE REPORT (S. 114-259)

1. Active Pharmaceutical Ingredients

The Committee is concerned that the FDA has not yet approved a list of active pharmaceutical ingredients [APIs] for use by compounding pharmacists pursuant to the Federal Food, Drug, and Cosmetic Act [FDCA]. Within 90 days of the enactment of this act, the FDA is directed to provide a timeline for when the remaining substances will be considered, and in the meantime re-consider its policy with regard to enforcement of the bulk drug substances provisions under section 503A.

FDA Response:

FDA will provide the requested report.

2. Artisanal Cheese

While the Committee appreciates the FDA's willingness to pause enforcement and reevaluate its standard regarding permissible levels of nontoxigenic *E. coli* in raw milk cheese, it remains concerned that this standard was developed in the absence of any published data from controlled studies describing either the process or rate of transfer of bacteria from the environment in the plant to the product. Therefore, the Committee directs the FDA to continue working with stakeholders to benefit from their expertise about safe cheese-making practices to achieve the mutual goal of food safety, and to provide to the Committee on Appropriations the results of the "Surveillance Sampling Program for Raw Milk Cheese."

FDA Response:

As the Committee notes, in February of 2016 the FDA paused its testing for generic *E. coli* in raw milk cheese as we consider the role of the generic *E. coli* standard in identifying and preventing insanitary conditions and food safety hazards for both domestic and foreign cheese producers. In July, we published findings from our FY 2014-2016 microbiological sampling assignment in which we analyzed raw milk cheeses that were aged for 60 days or longer: www.fda.gov/food/complianceenforcement/sampling/ucm510799.htm. Sampling assignments, such as this one, are an important part of our preventive approach to food safety by helping us identify hazards to minimize and enabling us to determine the prevalence of contamination in instances where we may not otherwise have enough data to do so.

We will use the results obtained under this assignment as part of our review of the role of testing for generic *E. coli* in identifying insanitary conditions for both domestic and imported raw milk cheese. FDA's deliberations include an extensive review of relevant scientific literature and stakeholder dialogue.

FDA looks forward to continuing to engage cheese industry stakeholders and experts in this scientific dialogue, and we welcome the opportunity to continue this dialogue with all

stakeholders to discuss the development and implementation of preventive controls for the manufacture of safe cheeses, with particular emphasis on the generic *E.coli* standard.

3. Atypical Actives

The Committee requests that the FDA provide an update on how it regulates “atypical actives.”

FDA Response:

FDA will provide the requested report.

4. Biosimilars

The Committee directs the FDA to provide no later than 30 days after enactment an estimated timeline by which the agency will finalize pending draft biosimilars guidance documents and an estimated timeline by which the agency will issue draft guidance on biosimilars topics, including, interchangeability, for which the agency has not published draft guidance.

In addition, the Committee recognizes that biosimilars offer an important opportunity for expanding the market and reducing costs for patients. The Committee urges the FDA to conduct outreach to external stakeholders including patient organizations on educating patients and professionals about biosimilars, with a focus on populations for which approved biosimilars are indicated.

FDA Response:

FDA will provide the requested report.

FDA remains committed to working with stakeholders, including drug manufacturers, prescribers, pharmacies, hospitals and health systems, informatics providers, and patient groups on this important issue.

5. Center for Safety and Nutrition Centers of Excellence

The Committee is aware of the important contribution of the FDA Center for Food Safety and Applied Nutrition’s Centers of Excellence [COEs] program in supporting critical basic research as well as facilitating the implementation of the FDA Food Safety Modernization Act. The Committee encourages the Agency to continue to fully utilize the COEs to accomplish these goals, and instructs that it enhance its level of support for FDA Food Safety Modernization Act activities.

FDA Response:

FDA appreciates the recognition of the importance of the COEs, their contributions to regulatory science, and encouragement of support for them.

6. Centers of Excellence in Regulatory Science and Innovation

The Committee is encouraged by the ongoing research and collaboration underway at the Centers of Excellence in Regulatory Science and Innovation program and commends the FDA for launching this program in 2011 and expanding it in 2014. As such, the Committee directs the Office of the Commissioner to use at least \$2,000,000 within existing funds to provide additional funding opportunities for the existing CERSI Centers to allow for the capitalization of ongoing studies and research.

FDA Response:

FDA appreciates the recognition of the importance of the CERSIs, their contributions to science in support of FDA's mission, and identification of resources for them. As directed, the Office of the Commissioner will use at least \$2,000,000 within existing funds to provide additional funding opportunities for the existing CERSI Centers to allow for the capitalization of ongoing studies and research.

7. Cosmetics

The Committee provides not less than \$11,700,000 for cosmetics activities, including not less than \$7,200,000 for the Office of Colors and Cosmetics [OCAC]. Funding for OCAC is for the direct support of the operation, staffing, compliance, research and international activities performed by this office.

FDA Response:

CFSAN will use funding for direct support of the operation, staffing, compliance, research, and international activities.

8. Cotton Ginning

The Committee is concerned about the impact of the "Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Food for Animals" final rule (80 FR 56170; September 17, 2015) on the cotton industry. The Committee notes post-harvest activity of ginning cotton does not transform the resulting cottonseed into a "processed food," and thus, cottonseed should fall within the definition of a "raw agricultural commodity" for purposes of rules promulgated pursuant to the FSMA. In addition, the Committee is concerned about the rationale for the definitions of "primary production farm" and "secondary activities farm" and how these definitions factor into the determination of operations either being exempt from or covered by certain requirements of the final rule. Therefore, the Committee directs the FDA to provide outreach and technical assistance to cotton ginning operations to assist them in complying with the final rule or subsequent guidance documents.

FDA Response:

FDA worked to harmonize the preventive controls rules for both human and animal food that were finalized in September 2015. In both of those regulations, "harvesting" is conducted by farms (primary production or secondary activities) or farm mixed-type facilities. Not all cotton

ginners are part of a farm, and when not conducted on a farm, the ginning of cotton is considered manufacturing, not harvesting. Because cotton ginning can result in manufacturing of animal food, cotton ginners that manufacture animal food for consumption in the U.S. are required to register and therefore are subject to certain provisions in the Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Food for Animals rule (PCAF rule).

FDA is aware of the cotton ginning industry's concerns regarding whether certain entities are classified as farms or facilities. We also are aware of their concern related to whether ginning results in a "processed food." FDA is looking at the farm definition, and will consider the concerns of the cotton ginning industry in that evaluation. To facilitate this effort, we extended the compliance dates for several provisions related to the farm definition, including extending compliance dates for the portion of the cotton ginning industry that is subject to the PCAF rule (please see the following webpage for more information about the compliance date extensions: www.fda.gov/Food/GuidanceRegulation/FSMA/ucm517545.htm). Compliance dates for the cotton ginning industry have been extended to January 28, 2019 or later depending on business size to provide FDA time to consider concerns raised by the cotton ginning industry.

FDA will continue to provide outreach and technical assistance, such as through meetings, to the cotton ginning industry to assist them in complying with the PCAF rule.

9. Diabetes

The Committee applauds the FDA for working with the diabetes community on clinical outcomes beyond hemoglobin A1c [HbA1c]. While HbA1c remains a fundamental measurement to assess the benefit of therapy for diabetes mellitus, regulatory decisions should be reached using the full range of outcomes that are important to people with diabetes. The Committee is pleased that the FDA will be holding a workshop focused on this topic in 2016 and encourages the Agency to incorporate the scientific learnings from that workshop into their decision-making so that important new, safe, and effective medical therapies can be made available to people with diabetes.

In addition, the Committee recognizes that being able to identify people at risk of developing type 1 diabetes could provide an opportunity to delay and eventually prevent the disease altogether. The appearance of certain islet autoantibodies in the serum of individuals increases the chance of developing type 1 diabetes at some point in the future. Therefore the Committee encourages the FDA to work with the Type 1 diabetes community on the assessment of potential diabetes biomarkers related to islet autoimmunity, which might help inform the design of clinical studies.

FDA Response:

FDA acknowledges that the benefits of antidiabetic therapies may extend beyond the benefits attributed to HbA1c reduction. FDA held a widely attended public workshop on the topic of "Outcomes beyond HbA1c" on August 30th, 2016. At this meeting, people with diabetes, patient advocates, healthcare providers, diabetes researchers and manufacturer of diabetes related-products proposed a broad range of measures centered on the patient experience that

could potentially serve to detect clinical benefits of antidiabetic therapies not captured by HbA1c. To incorporate the learning from this workshop, the FDA is using the Critical Path Innovation Meeting program and the Drug Development Tools Qualification Program to encourage stakeholders to propose specific measures that could be used to reliably capture one or more benefit with the goal of incorporating these measures in studies used for drug development and in decision-making. Related to benefits of antidiabetic therapies that extend beyond the benefits attributed to HbA1c reduction, the FDA approved, in 2016, the first ever antidiabetic therapy for Type 2 diabetes mellitus that was demonstrated to also reduce the risk of cardiovascular death in patients with Type 2 diabetes and heart disease.

FDA acknowledges that being able to reliably identify people at risk of developing Type 1 diabetes with prognostic immune markers could help inform the clinical studies for development of therapeutics aiming to delay or prevent Type 1 diabetes onset. FDA is partnering with the Critical Path Institute and the Type 1 diabetes community on a project whose objective is to leverage existing data for the purpose of qualifying the use of diabetes biomarkers related to islet autoimmunity as prognostic markers for Type 1 diabetes. Where appropriate, companies may still discuss specific drug development proposals for therapeutics aiming to delay or prevent Type 1 diabetes that involve use of one or more of these biomarkers in the setting of FDA's formal meetings with industry under the Investigational New Drug application mechanism.

10. Donor Milk Supply

The Committee is aware of the growing commercial human milk industry, and its importance to, in particular, preterm infants. The Committee is also aware that the FDA has had discussions with the industry regarding the need for adequate safeguards to ensure the safety and nutritional quality of the donor human milk supply. The Committee directs FDA to report on its efforts to implement regulations to protect a safe and stable human milk supply.

FDA Response:

Products containing donor human-milk-based products are generally regulated as foods. Certain products may also be regulated under more specific requirements, such as those for exempt infant formula (i.e., infant formula that is represented and labeled for use by infants who have inborn errors of metabolism or low birth weight, or who otherwise have unusual medical or dietary problems). The FDA Food Safety Modernization Act (FSMA) significantly strengthened FDA's authorities over the food safety system and requires food facilities to establish and implement hazard analysis and risk-based preventive controls for human food.

FDA's rule implementing mandatory preventive controls for human food was finalized in 2015, and the compliance dates for some businesses began in September 2016. Facilities producing human-milk-based food products are subject to FSMA's risk-based mandated inspection frequencies. High-risk domestic facilities will be inspected every three years and non-high risk facilities every five years.

Donor human milk could, in certain circumstances, also be regulated under additional specific requirements, such as those for exempt infant formula. Facilities that produce exempt infant formula are inspected annually.

For non-commercial use, some hospitals have milk banks for use in neonatal intensive care units; other hospitals obtain milk from the Human Milk Banking Association of North America (HMBANA). Although the majority of the donor human milk from HMBANA milk banks is distributed to hospitals, it is also distributed to infants in the home who need donor human milk because of medical conditions such as formula intolerance or feeding issues related to prematurity. When possible, milk banks serve healthy babies who have been adopted or are otherwise not able to get their own mother's milk. HMBANA sets standards and guidelines that its member milk banks can follow. Among other things, those guidelines provide recommendations for donor screening and pasteurization.

11. Drug Shortages

The Committee requests that the FDA report on how it works with manufacturers to facilitate timely communication to the field on the availability of drugs in shortage, as well as its processes for the completion of drug application reviews and facility inspections during times of or risk of critical drug shortage.

FDA Response:

FDA will provide the requested report.

12. Duchenne Muscular Dystrophy

The Committee is encouraged that the FDA has the tools, authorities, and latitude necessary to review and approve safe and effective treatments for rare diseases, such as Duchenne Muscular Dystrophy, as efficiently as possible. In particular, the Committee is aware that the use of intermediate clinical endpoints [ICE] may be an appropriate approach as they have been in similar deadly diseases with dire unmet need, such as HIV and cancer.

FDA Response:

FDA is committed to engaging with patient groups to receive valuable input during the evaluation of the medical needs of patients with rare diseases whenever appropriate. We appreciate the proposed guidance that members of the Duchenne muscular dystrophy (DMD) community submitted to FDA in June 2014. FDA announced the DMD community's guidance through a Federal Register notice on September 4, 2014, to seek additional input and public comment. FDA carefully considered the consortium's guidance and public comments received in response to it in writing the agency's own draft guidance.

The draft guidance for industry, "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment," was released in June 2015, and a 60-day comment period was provided. We are currently reviewing the comments received and plan to issue a final guidance following review of those comments. The purpose of the guidance to industry is to assist sponsors in the clinical development of drugs for treating X-linked Duchenne muscular dystrophy and related dystrophinopathies, discuss various pathways to approval including the use of intermediate clinical endpoints, and to serve as a focus for continued discussions on this topic.

13. Drug Vial Sizes

The Food and Drug Administration is responsible for approving vial sizes and fill volumes for injectable drug products before products come to market, in a manner that balances multiple considerations related to safe use and administration of the product. In 2015, the FDA issued guidance documents for industry on this matter. Given that many factors play a role in FDA's assessment of vial sizes for injectable drug products, the Committee directs the FDA to provide a report to Congress within 180 days of enactment with recommendations on how the FDA may assist in addressing concerns about appropriate vial sizes and fill volumes from a safety perspective, to ensure that patients are receiving the appropriate care.

FDA Response:

FDA will provide the requested report.

14. Experimental Drugs for Terminally Ill Patients

The Committee directs the FDA to report on efforts to increase patient access to experimental drugs for terminally-ill patients.

FDA Response:

FDA will provide the requested report.

15. FDA Food Mission

The Committee requests information on FDA's current nutrition activities and resources.

FDA Response:

FDA's Foods and Veterinary Medicine (FVM) Program helps to ensure that the nation's food supply is wholesome, that food is labeled truthfully and in a manner that is not misleading, and that nutrition labeling is informative and accurate. The FVM Program also promotes a nutritious food supply that ultimately contributes to the risk reduction of diet-related chronic disease. The FVM Program, including Center and Field activities, spent \$28.9 million on nutrition-related priorities in FY 2016.

16. Food Contact Notification User Fees

The Committee recommendation does not include proposed user fees.

FDA Response:

FDA acknowledges the Committee's recommendation on the proposed user fees.

17. Food Packaging

The Committee encourages FDA to increase the involvement of experts in endocrinology as FDA continues to evaluate the chemical BPA and similar alternatives such as BPS as it relates to health safety of human exposure through food packaging. Evaluations shall include specific focus on the long-term low dose exposure that these chemicals have on the endocrine system

FDA Response:

FDA agrees that endocrinology is an important discipline for the evaluation of chemical safety. FDA personnel have expertise in a broad range of scientific and medical fields, including endocrinology, for assessment of relevant chemical safety issues. As an example, in the fall of 2014, FDA experts specializing in toxicology, analytical chemistry, endocrinology, epidemiology, and other fields completed a four-year review of more than 300 scientific studies on the safety of BPA. Among other factors, this review evaluated available information on long-term low dose exposure and the endocrine system. Reports from this team of experts can be found at:

www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm166145.htm

and

www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm064437.htm.

18. Food Traceability

The FDA announced two pilot projects on September 7, 2011 pursuant to section 204 of the Food Safety Modernization Act, which required pilot projects for improving product tracing along the food supply system and establishment of recordkeeping requirements for high-risk foods to help in tracing products. The pilots were conducted by the Institute of Food Technologists, in consultation with industry sectors, USDA, State agencies and consumer groups, and the resulting report was released on March 4, 2013. The Committee notes that industry and government continue to pursue their traceability goals on separate tracks and with little collaboration. The Committee further notes that no report has been issued pursuant to section 204(a) of the act, which directs the Secretary to report to Congress on the findings of the pilot projects, and the Committee directs the Secretary to issue such report. Furthermore, the Committee notes that the Secretary has failed to propose a rulemaking to establish the recordkeeping requirements as required by section 204(d) of the act. The Committee directs the FDA to collaborate with science-based international and industry-led food traceability initiatives of the type recommended by the pilot projects. In addition, the Committee directs the Commissioner to make publicly available information on FDA's efforts to encourage the work of science-based international and industry-led food traceability initiatives.

FDA Response:

FDA provided the report to Congress on the two traceability pilots on January 5, 2017. A copy of the report can be found at:

www.fda.gov/downloads/Food/GuidanceRegulation/FSMA/UCM540940.pdf. In the report,

FDA provides recommendations that cover a broad spectrum of activities including, but not limited to, identifying uniform key data elements, finding ways to link foods as they move

through the supply chain, and collaborating with industry and encouraging proactive industry-led efforts to improve traceability. The report also outlines FDA's strong historical engagement with industry on this topic, including collaboration on pilot projects and communications through public meetings. Consistent with our past practices, FDA will continue to share with the public, such as during meetings and conferences – information on traceability projects and other collaborations with our stakeholders. FDA remains committed to working with industry to improve traceability, such that a contaminated food can more rapidly be traced to its source and removed from the marketplace in order to prevent consumers from becoming ill.

19. Foreign High Risk Inspections

The bill provides an additional \$3,000,000 and a total of \$8,000,000 for the FDA's Office of Global Regulatory Operations and Policy to enhance the compliance of foreign manufacturers and exporters of food, medical devices and pharmaceuticals through on-site verification.

FDA Response:

FDA's Office of Global Regulatory Operations and Policy intends to spend the amount directed by Congress to bolster the important ongoing development and utilization of a targeted, risk-based, and efficient inspection model for foreign high risk facilities. The funding will support efforts to develop key systems, processes, and data sources in different commodity areas including food safety and medical products. The funding will also support enhancements to FDA's ability to identify risk indicators in existing data sets.

These efforts may include mutual reliance or other methods to leverage inspection and site data from foreign regulators. Additionally, these efforts will support the incorporation of commercially available information on high-risk establishments for onsite verifications. The increased funding will drive significant progress in achieving these multi-year objectives.

20. Human Tissue Models, Including 3D Models

The Committee is aware that bioengineered human tissue models hold the promise of improving the drug discovery process by enhancing the ability to predict potential safety risks during preclinical testing and post market safety of pharmaceutical products, thereby minimizing the potential risk of adverse toxicological outcomes to patients during clinical trials and post-approval use. The Committee directs the Secretary to prepare a report, with input from the Office of Regulatory Science and Innovation and the National Center of Toxicology Research, on how to accelerate adoption of predictive bioengineered human tissue models when used in combination or in lieu of animal testing models pre and post market approval. The Committee directs the Secretary to report recommendations to the House and Senate Appropriations Committees within 180 days of enactment of this Act.

FDA Response:

FDA is supportive of the Committee's recommendation that a report be developed to address how to accelerate adoption of predictive bioengineered human tissue models when used in combination or in lieu of animal testing models before and after market approval and will support the Secretary in preparation of such a report.

21. In Silico Clinical Trials

In Silico clinical trials use computer models and simulations to develop and assess devices and drugs, including their potential risk to the public, before being tested in live clinical trials. Advanced computer modeling can also be used to predict how a drug or device will behave when deployed in the general population, thereby protecting the public from the unintended consequences of side effects and drug interactions. In Silico trials protect public health, advance personalized treatment and can be executed quickly and for a fraction of the cost of a full scale live trial. The FDA has advocated the use of such systems and utilized them with success in the past. Therefore, the Committee strongly encourages the FDA to make greater use of In Silico trials for devices and drug therapies before they are released for live clinical trials.

FDA Response:

FDA acknowledges the benefits to public health provided by in silico clinical trials, and has previously advocated for their use as one of many research tools. Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study design strategies, so that safe and effective new therapeutics can advance more efficiently, from preclinical studies through clinical trials to market. The efforts in modeling and simulation are enabled through multiple collaborations with external parties that provide additional expertise and infrastructure to advance the development of innovative state-of-the-art technologies.

FDA advises sponsors on the use of modeling and simulation to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms. Some computational models are firmly embedded in the product review process and supported by guidances, while others are used as needed (fit-for-purpose) or in a research capacity to help inform regulatory decisions.

FDA is also collaborating, both internally and externally (with both Investigational New Drug application sponsors and New Drug Application stakeholders, researchers, and other regulatory bodies), to maximize the use of modeling and simulation to complement clinical trials or to improve their design and success, including – but not limited to – comparative predictions of Phase 3 responses across a novel therapeutic class and replacement of clinical studies with in silico modeling for cardiac safety testing.

In addition FDA is actively working to explore modeling approaches and enhance their regulatory impact through the Agency's Scientific Computing Board whose goal is to advance science, streamline operations, and strengthen FDA's overall effectiveness. FDA drug modeling reviewers have also actively engaged with device modeling efforts to build regulatory models for product design and evaluation, including the development of a digital library of models and a family of "virtual patients" for device testing.

22. In Vitro Clinical Trials

In vitro clinical trials use specimens collected from patients to test how a particular cancer or disease will react to a specific therapy or combination of therapies. This personalized approach to treatment can improve a patient's quality of life by increasing the likelihood that physicians and researchers will find the proper combination of drugs uniquely suited to treat that individual's illness. An emerging new scientific methodology, In Vitro trials allow researchers to

test therapeutics and treatment strategies on living human tissues without the risks posed by traditional whole patient clinical trials. Personalized treatment through In Vitro trials dismantles the “one size fits all” approach to care and enables medical professionals to diagnose and treat patients in a more efficient and effective way. Accordingly, the Committee strongly encourages the FDA to make greater use of In Vitro clinical trials for Investigational New Drug applications and general therapeutic indications, especially as it relates to complicated cancers and other common disease States.

FDA Response:

FDA acknowledges the benefits to public health provided by In Vitro trials, and the potential to provide more personalized medical treatment options for patients. The Critical Path Innovation Meeting program, launched by FDA in 2013, allows drug developers and other stakeholders to discuss new and emerging technologies with FDA. These meetings have included topics related to In Vitro trials to identify suitable combination therapies to take into clinical trials. FDA will continue to engage stakeholders through this mechanism to discuss such technologies. Where appropriate, companies may still discuss specific drug development proposals involving these technologies in the setting of FDA’s formal meetings with industry under the Investigational New Drug application.

In addition, consortia and other stakeholders may interact with FDA via the Drug Development Tools Qualification Program to the extent that a particular technology platform is being formally developed to support regulatory decision-making. FDA has received submissions involving In Vitro trials, and will continue to engage with sponsors of drug development tools to advance In Vitro trials into drug development.

23. Listeriosis

Listeriosis is a serious illness that is usually caused by eating food contaminated with the bacterium *Listeria monocytogenes*. The disease primarily affects older adults, pregnant women, newborns, and adults with weakened immune systems. To better understand the risk of listeriosis associated with the consumption of certain foods, the FDA has conducted or is conducting risk assessments on ready-to-eat foods, soft ripened cheeses, smoked finfish, and retail delicatessens. These risk assessments have been used to protect and enhance the public health.

The FDA uses risk analysis to ensure that regulatory decisions about foods are science-based and transparent. For the first time, the consumption of certain frozen vegetables has been linked to a multi-state outbreak of listeriosis. Because of this outbreak, the need to protect the public health, and to ensure science-based and transparent regulatory decisions, the Committee encourages the FDA to conduct a quantitative risk assessment of the relative risk to public health from foodborne *Listeria monocytogenes* among frozen vegetables and other frozen foods currently considered not ready-to-eat.

FDA Response:

FDA determines the risk associated with *Listeria monocytogenes* in a frozen food, such as a frozen vegetable, on a case-by-case basis depending on a number of factors, including whether it supports the growth of the pathogen when thawed and how the frozen food is commonly

handled. Some frozen vegetables present minimal risk to consumers because these vegetables are commonly held frozen, cooked from a frozen state, and immediately consumed. By contrast, some frozen vegetables can be thawed and used without cooking in salads, whether in commercial salad bars or in the home; and some recipes available to consumers describe the preparation of products using frozen vegetables that are thawed but not cooked. Where a frozen food that supports growth of *L. monocytogenes* is thawed and held for considerable time at refrigerated or room temperature, such as on a salad bar, it may pose a risk to consumers because it has not been subject to cooking that would kill the pathogen and it will be held under conditions that allow pathogen growth to occur.

Every few years, FDA identifies new vehicles for *L. monocytogenes* illness among foods with no known prior history of contamination or epidemiological link to listeriosis, and some foods with limited histories of contamination can prove to be higher risk than previously thought. For example, in 2016, CDC identified a multistate outbreak of listeriosis linked to frozen vegetables by epidemiologic and laboratory evidence. We anticipate that the pattern of discovering new food vehicles will continue, if not hasten, with the advancement of whole genome sequencing in connecting known clinical illnesses with the foods responsible for those illnesses.

FDA is not aware of the type of comprehensive up-to-date survey data that would be needed to develop a quantitative risk assessment for foodborne *L. monocytogenes* in frozen vegetables; therefore, FDA would have to conduct its own survey prior to conducting such a risk assessment or to commission another organization to conduct such an assessment. For example, a 2003 Quantitative Assessment of Relative Risk to Public Health from Foodborne *Listeria monocytogenes* Among Selected Categories of Ready-to-Eat Foods -- jointly developed by FDA, the Centers for Disease Control and Prevention, and the USDA's Food Safety and Inspection Service -- took four (4) years to complete, beginning with a *Federal Register* notice of intent issued in 1999 and culminating in completion of the final assessment in 2003.

24. Mammography Quality Standards Act

The Committee recommendation includes full funding as requested for implementation of the Mammography Quality Standards Act. This program sets national quality standards for mammography facilities, equipment, personnel and operating procedures, and has improved the quality of mammography and made mammograms a more reliable tool to detect breast cancers.

FDA Response:

FDA intends to fully fund the MQSA program.

25. Medical Devices

The Committee is concerned about the lack of transparency and consistency with the medical device facility inspection process. This often leads to inefficiencies and inconsistencies in the inspection process. The Committee urges the agency to work with stakeholders and Congress to improve the facility inspection process. Potential process improvements may include, but are not necessarily limited to, more timely and frequent communications related to inspection observations and remediation plans, as well as changes to the way medical device Export

Certificates (e.g., Certificate to Foreign Government, etc.) are affected by FDA Observational Findings following a facility inspection.

FDA Response:

A majority of both domestic and foreign device inspections involve four or fewer days on-site. There are many inspections that conclude on the same day as arrival. Investigators follow the same procedures, which are publicly available, when conducting a domestic inspection as they do for a foreign inspection. The Investigations Operations Manual, which is publicly available, states that every reasonable effort should be made to discuss all observations with the management of the establishment as they are observed, or on a daily basis, to minimize surprises, errors and misunderstanding when the 483 is issued. Inspectional staff will be reminded of these requirements.

FDA is currently addressing domestic inspection times through improved internal procedures and through Program Alignment, which will take effect on May 15, 2017. Program Alignment is FDA's reorganization of its inspection program to a commodity-based and vertically-integrated structure. It is intended to improve consistency by focusing on investigators' training and workload on one product area; for example, only device investigators will inspect device establishments and drug investigators will inspect drug establishments.

FDA has indicated its willingness to hold a public meeting to gather input from affected stakeholders about improvements to the device inspections process. FDA is working with HHS to review legislative proposals intended to help streamline the device inspections process and to improve the process for issuing export certificates.

26. Medical Device Performance

The Committee is aware that each year the FDA is required to submit a report to Congress regarding performance goals for user fees paid by medical device manufacturers. However, the Committee is concerned that FDA may not be providing information about how the FDA is meeting timelines established in law by Congress. The Committee directs the FDA to provide a report to the Committee within 90 days of the date of enactment including performance information for statutory timelines for medical devices, specifically: the number of de novo requests under 513(f)(2) for which FDA has met the 120 day statutory requirement, and the total number of de novo requests submitted; the number of requests for classification under 513(g) and the number for which FDA has met the 60 day statutory requirement; and, the number of orders for postmarket device surveillance under 522 for which the FDA has responded within 60 days of receipt of such plan.

FDA Response:

FDA submits an annual report to Congress as well as provides quarterly reporting to the industry and the public. Under the MDUFA IV agreement submitted to Congress in January 2017, FDA would report new information to Congress, industry, and the public, including its performance on de novos.

27. Medical Foods

The Committee urges the FDA to be more active in engaging external stakeholders on best practice standards for medical foods that are based upon the Generally Recognized as Safe [GRAS] status. The Committee requests the FDA work with external stakeholders in forming a framework for a distinct regulatory pathway for medical foods that does not encumber its progress towards approval for patient use.

FDA Response:

FDA recognizes that medical foods serve a critical role in the lives of patients with inherited metabolic disorders such as phenylketonuria (PKU). The agency's goals for medical foods include staying abreast of the science in this rapidly evolving field; working to ensure the availability of safe and appropriately labeled; and providing sound guidance to patients, healthcare providers, and industry. For example, FDA provided stakeholders an updated medical foods guidance in May 2016.¹⁰⁶

DA prioritizes communication and collaboration with medical food stakeholders on scientific issues. For example, a recent NIH study revealed that a medical food intended for a single specific metabolic disorder was being inappropriately used to treat patients with a combination metabolic disorder, resulting in adverse effects. FDA, NIH, and a manufacturer of one such product collaborated on the matter, which led to the manufacturer changing the product labeling to warn healthcare practitioners against its use for the specific combination disorder at issue. The manufacturer and NIH agreed to continue working in partnership to further study that disorder (and other related metabolic disorders), with FDA providing regulatory knowledge and guidance as needed.

We note that issues pertaining to GRAS status are only some of the many potential issues that can affect medical foods, and that GRAS status has no bearing on whether a product meets the statutory definition of a medical food. Further, we note that medical foods are not subject to an approval process. Rather, medical foods are a type of conventional food.

28. Medical Gases

The Committee is significantly concerned that FDA has not initiated rulemaking, nor listed such rulemaking as a priority in the Unified Agenda, to address numerous longstanding regulatory issues for medical gases despite the statutory requirement section 1112 in FDASIA (Public Law 112–144) to issue a final rulemaking addressing all necessary changes for medical gases by July 9, 2016. The Committee disagrees with the FDA report to Congress sent on June 29, 2015, and believes that FDA must address medical gas regulatory issues with a new rulemaking amending the Federal drug regulations. Therefore, FDA shall issue final medical gas regulations as required by FDASIA not later than July 9, 2016. If FDA determines that it is a more efficient use of resources, it should incorporate by reference a voluntary consensus standard by an ANSI-accredited standard development organization as required by the National Technology Transfer and Advancement Act of 1995 (Public Law 104–113), and the Office of Management and

¹⁰⁶ Guidance for Industry: Frequently Asked Questions About Medical Foods; Second Edition, www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm054048.htm

Budget [OMB] Circular A–119. If FDA fails to issue final regulations with respect to medical gases by the statutory deadline, the Agency shall incorporate by reference voluntary consensus safety and labeling standards developed by an ANSI-accredited standard development organization until such time as the Agency issues final regulations consistent with section 1112 of Public Law 112–144.

FDA Response:

FDA issued the final rule “Medical Gas Containers and Closures: Current Good Manufacturing Practice Requirements,” on November 18, 2016 (81 FR 81685). This final rule (which revised warning statements for medical gases and required measures intended to reduce the likelihood of medical gas mix-ups) satisfies the FDASIA medical gas rulemaking requirement, though FDA may undertake additional rulemaking on medical gases as needed.

FDA understands that industry stakeholders believe that FDA should promulgate a separate regulatory scheme specific to medical gases, despite the Agency’s determination (explained in its 2015 report to Congress on this topic) that extensive rulemaking in this area is unnecessary. However, FDA remains convinced that we can work within the existing regulatory framework to set clear and appropriate regulatory expectations for the production and distribution of medical gases without extensive additional rulemaking. FDA recently made revisions to the medical gas inspection program (completed in 2015), and is very far along in the process of producing revised guidance on current good manufacturing practices applicable to medical gases.

FDA will, of course, undertake targeted rulemaking on medical gases to address any significant public health issues that arise, or to satisfy statutory rulemaking requirements – as demonstrated by the final rule published in November 2016. However, FDA continues to believe that the separate regulatory scheme for medical gases sought by industry stakeholders is unnecessary.

FDA also has significant concerns with any proposal mandating that FDA incorporate medical gas industry standards by reference. First, incorporation by reference requires notice-and-comment rulemaking, with all of the resource burdens rulemaking entails. Furthermore, the proposal to incorporate by reference “voluntary consensus safety and labeling standards” would first require such standards to be developed, as it does not appear that any currently exist. Rather, the safety and labeling standards industry has sought to have FDA incorporate by reference were created entirely by the industry, with no FDA involvement. In fact, these “standards” are largely identical to the dozens of new regulations industry proposed during the 2013 FDASIA regulation review, and which FDA determined were generally not needed. FDA is not opposed to referencing specific targeted standards co-developed by FDA and the medical gas industry (provided FDA agrees such standards meet regulatory and public health needs) and engaging in rulemaking as necessary and appropriate. However, FDA sees significant legal, policy, logistical, and resource concerns with adopting unvetted industry standards by reference.

Finally, FDA is concerned with the precedent that would be set by creating a separate regulatory scheme for a given product class. In general, FDA believes it is much more efficient to rely upon the general regulatory scheme applicable to all drug products, and to provide class-specific recommendations through guidance and other non-rule-making means.

Accordingly, FDA's position continues to be that the extensive rulemaking sought by industry is not necessary.

29. Nanotechnology

The Committee recognizes the increased capabilities that FDA has developed to study environment, health, and safety of nanomaterials within FDA's Jefferson Laboratory Campus, including the National Center for Toxicological Research, and its consolidated headquarters at White Oak, Maryland. The Committee expects FDA to continue to support collaborative research with universities and industry on the toxicology of nanotechnology products and processes in accordance with the National Nanotechnology Initiative Environment, Health, and Safety Research Strategy as updated in October 2011.

FDA Response:

FDA continues to enhance capabilities to understand the health impact and safety of nanomaterials through staff training, continued research into the safety and disposition of nanomaterials in various products, increased collaboration with government agencies — both national and international — and participation in standards-development activities. FDA continues its efforts to enhance its nanomaterials research infrastructure. Since 2011, the CORES research program funded a total of 36 projects and is part of FDA's Nanotechnology Regulatory Science Research Plan. Together with the advanced Nanocore infrastructure at the Jefferson Laboratories campus and the facilities at the White Oak campus, FDA is able to conduct research to accurately characterize, detect, and quantify nanomaterial in FDA-regulated products to help assess safety and inform risk assessment. FDA's Nanotechnology Task Force is committed to advancing nanotechnology research and collaborations.

FDA continues to engage with industry and other agencies through the National Nanotechnology Initiative (NNI), including participation in the US-EU Communities of Research, Indo-US Science and Technology Forum, Nanotechnology for Healthcare Conference, and collaborations with the Consumer Protection Safety Commission, National Institute of Environmental Health Sciences/National Toxicology Program, and the National Cancer Institute.

The 2016 Global Summit on Regulatory Science focused on "Nanotechnology Standards and Applications," and was hosted by FDA/NCTR and Arkansas Research Alliance. There were other U.S. government agencies in attendance at the Summit — held on the NIH campus — as well as from 19 countries. This annual Summit is held in cooperation with the European Union and global regulatory and standards agencies to discuss the standards methodologies and standards that are helpful for regulatory review. The outcome from the Summit was a list of standards in nanotechnology that are relevant to drugs, devices, and consumer products. FDA will also continue to engage industry through the standards-development organizations and develop relevant and consensus based standards that can help regulatory reviews.

30. National Antimicrobial Resistance Monitoring System

The Committee recommendation includes \$10,800,000 for the National Antimicrobial Resistance Monitoring System, equal to the level provided in fiscal year 2016.

FDA Response:

FDA will provide funding equal to FY 2016 levels as recommended by the Committee.

31. Olive Oil

The Committee directs the FDA to take a sampling of off-the-shelf olive oil bottles offered for sale to consumers to determine if it is adulterated with seed oil, pursuant to Section 342 of the FDCA, and report to Congress within 270 days on its findings.

FDA Response:

In 2014, FDA performed a survey of olive oil products available to consumers within the United States, and included a cross-section of domestic and imported products in the survey. FDA used USDA grading standards in the assessment and used an analytical methodology capable of detecting 10 percent seed oil adulteration. Out of 88 products surveyed, only 3 showed evidence of adulteration. This work was published in a peer-reviewed publication^{1,2}. FDA continues to develop better methods that may be able to detect adulteration beyond gross addition of seed oils^{3,4}. FDA plans to continue to monitor the marketplace for adulterated olive oil products to ensure consumer safety and proper labeling of imported olive oil.

1. Authenticity Assessment of Extra Virgin Olive Oil: Evaluation of Desmethylsterols and Triterpene Dialcohols; Srigley, CT; Oles, CJ; Kia, ARF; Mossoba, MM; JOURNAL OF THE AMERICAN OIL CHEMISTS SOCIETY; 93(2); 2016; pp: 171-181. (DOI: 10.1007/s11746-015-2759-4)
2. Authenticity Assessment of Extra Virgin Olive Oil, part 2. Evaluation of fatty acids and triacylglycerols; manuscript in preparation, 2017.
3. Nontargeted, Rapid Screening of Extra Virgin Olive Oil Products for Authenticity Using Near-Infrared Spectroscopy in Combination with Conformity Index and Multivariate Statistical Analyses; Karunathilaka, SR; Kia, ARF ; Srigley, C (Srigley, Cynthia); Chung, JK; Mossoba, MM; JOURNAL OF FOOD SCIENCE; 81(10); 2016; pp C2390-C2397. DOI: 10.1111/1750-3841.13432
4. Developing FT-NIR and PLS1 Methodology for Predicting Adulteration in Representative Varieties/Blends of Extra Virgin Olive Oils; Azizian, H; Mossoba, MM ; Fardin-Kia, AR ; Karunathilaka, SR; Kramer, JKG; LIPIDS; 51(11); 2016, pp 1309-1321 (DOI: 10.1007/s11745-016-4195-0).

32. Opioid Overdose Prevention

The Committee is very concerned about the ongoing prescription opioid abuse epidemic, and is additionally concerned by FDA's decision in August 2015 to approve OxyContin for pain management in children as young as 11 years old. As the Agency that oversees the approval of these drugs, the FDA has a responsibility to consider the public health impact of opioid abuse

and overdose death. Therefore, the Committee directs FDA to continue implementing its opioids action plan announced in February 2016 to take concrete steps toward reducing the impact of opioid abuse on American families and communities, and to strongly consider the danger of addiction and overdose death associated with prescription opioid medications when approving and regulating the manufacturing, marketing and distribution of opioid medications. This plan should include policies aimed at reversing the epidemic while still providing patients access to effective pain relief. Finally, the FDA is directed to refer any new drug application for an opioid submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act to an advisory committee for their recommendations prior to approval, unless the FDA finds that holding such advisory committee meeting is not in the interest of protecting and promoting public health.

FDA Response:

FDA will continue to implement its opioid action plan announced in February 2016, and will continue to follow section 106 of the Comprehensive Addiction and Recovery Act (CARA) concerning this action plan. Specifically, FDA will convene an expert advisory committee before approving any New Drug Application for an opioid unless FDA determines that such referral is not required, as provided in CARA section 106(a)(1)(B) (“Public health exemption”). Additionally, the Pediatric Advisory Committee will make recommendations regarding a framework for pediatric opioid labeling before any new pediatric labeling is approved. Finally, FDA will continue to appropriately consider the public health consequences of opioid abuse (including addiction and overdose) when regulating opioid medications.

33. Over-the-Counter Drugs

The Committee directs the FDA provide a report on the funding levels put to OTC Monograph issues for the past 10 years (fiscal year 2006–2016).

FDA Response:

FDA will provide the requested report.

34. Parallel Review Pilot

The Committee directs the FDA to report on plans to extend the pilot and steps the agency will take to encourage more manufacturers to utilize the pilot, including considerations for manufacturers choosing the 510(k) clearance pathway and for novel products deemed covered by CMS but that warrant evaluation to ensure the appropriate level of coverage.

FDA Response:

FDA and CMS have already made the pilot Parallel Review Program into a permanent program, as stated in the published guidance 81 FR 73113-15 (Oct. 24, 2016). CMS, rather than FDA, determines the appropriate level of coverage. FDA and CMS continue to work together to balance sponsor evidence requirements to find the least burdensome approach to evidence collection.

35. Patient Focused Drug Development Initiative

The Committee applauds FDA's efforts to engage external and patient stakeholders through FDA's Patient Focused Drug Development initiative which includes convening disease-specific public meetings, publication of Voice of the Patient reports for each meeting, and welcoming stakeholders to conduct externally-led Patient Focused Drug Development Meetings. The Committee encourages FDA to continue working with external stakeholders to develop a strategic action plan in follow up to these activities.

FDA Response:

FDA values the experiences and perspectives of patients and caregivers. Under PDUFA V, FDA will have conducted 24 disease-specific patient-focused drug development meetings to systematically obtain patient and caregiver input on a range of disease areas. To help expand the benefits of FDA's Patient-Focused Drug Development (PFDD) initiative, FDA is also welcoming patient organizations to identify and organize patient-focused collaborations (e.g., externally-led PFDD meeting) to generate public input on other disease areas.

FDA will continue efforts to enhance the incorporation of the patient's voice into drug development and regulatory decision-making. For PDUFA VI reauthorization, FDA and industry reached agreement on a set of proposed enhancements to facilitate the advancement and use of systematic approaches to collect and utilize robust and meaningful patient input that can inform drug development. The 21st Century Cures Act also has several FDA requirements on Patient-Focused Drug Development, which are mostly aligned with the PDUFA VI proposed recommendations.

36. Pediatric Device Consortia Grants

The Committee is pleased that the nine FDA-funded Pediatric Device Consortia have assisted in the development of more than 650 proposed pediatric medical devices since its inception in 2009, as well as promoting job-growth in the healthcare sector, and as such, continues to support this critical effort. The program funds consortia to assist innovators in developing medical and surgical devices designed for the unique needs of children that often go unmet by devices currently available on the market. The Committee recommendation includes \$5,000,000 for Pediatric Device Consortia Grants.

FDA Response:

The PDC Grant Program continues to successfully support the development of pediatric medical devices and fulfill unmet needs in the pediatric population. Since the program's inception in 2009, the pediatric device consortia have advised innovators on more than 900 potential pediatric devices – and assisted on more than 300 projects just this past year alone. As a result of funding advice provided by the consortia, more than \$ 110 million of additional funds have been raised to advance pediatric device projects affiliated with the consortia. In the last 4 years, more than ten PDC-assisted pediatric medical devices have become available for use in pediatric care, including TIVA, a needle-free blood collection device, and SleepWeaver Advance Pediatric CPAP Mask. The FDA recognizes the value of the Pediatric Device Consortia in supporting the pediatric medical device ecosystem toward development and innovation for children. The FDA

anticipates funding the PDC at the appropriated level for the upcoming year, consistent with prior years.

37. Proprietary Information

The Committee is concerned with requirements in the Nutrition Facts proposed rule that may cause some manufacturers to disclose proprietary records. Therefore, the Committee urges the FDA to ensure that steps are imposed to protect the security of trade secrets and commercial confidential information if it is provided to FDA.

FDA Response:

FDA issued a final rule for the revision of the Nutrition Facts and Supplement Facts labels on May 27, 2016. The final regulation for the Nutrition Facts label does not require firms to submit information to FDA. As a result, the circumstances under which FDA would review company information are limited to inspection activities associated with verifying compliance. However, we are aware of concerns regarding the safeguarding of information that FDA might review or collect during an inspection, and FDA is training inspectors regarding those concerns. Those records requirements are only for foods for which an adequate analytical method to verify the compliance of a nutrient declaration is not available. The records will allow us to verify the declared amount of each such nutrient and that such amount is truthful and not misleading. Thus, the records requirements will help in the efficient enforcement of the Federal Food, Drug, and Cosmetic Act. On January 5, 2017, FDA announced the availability of draft guidance with a request for comment, entitled Questions and Answers on the Nutrition and Supplement Facts Labels Related to the Compliance Date, Added Sugars, and Declaration of Quantitative Amounts of Vitamins and Minerals. Among other things, that guidance, when final, will provide further guidance to industry on the types of records required and how the relevant information can be acquired.

The recordkeeping requirements in the May 2016 final rule are intended to be flexible in that they do not require a specific document to be retained, nor do they require information on proprietary recipes or overall formulations. Instead, the records requirements seek specific content information only for certain nutrients for which no analytical method is available, and this information could be provided in various forms by the manufacturer. Thus, the records required to verify the accuracy of the declared amount of these specific nutrients can include records that do not include proprietary information.

Furthermore, even if a manufacturer's records contained confidential commercial information or trade secret information, or a manufacturer believed that certain information should be protected from public disclosure, there are safeguards to protect against public disclosure of that information and mechanisms that a manufacturer can use to assert that certain information should be protected from disclosure. FDA protects confidential information from disclosure, consistent with applicable statutes and regulations, including 5 U.S.C. 552(b)(4), 18 U.S.C. 1905, and 21 CFR part 20. For example, our regulations pertaining to disclosure of public information, at 21 CFR part 20, include provisions that protect trade secrets and commercial or financial information which is privileged or confidential. If a manufacturer provides proprietary

recipe information to show compliance with the nutrition label regulation, the manufacturer should mark the information as such before providing any requested records to FDA.

38. Seafood Advisory

The Committee directs the FDA ensure that pregnant women receive final guidance on nutrition advice for what seafood is safe and healthy to consume that is consistent, understandable, and based on the FDA’s latest scientific review of the net effects of seafood consumption.

FDA Response:

On January 18, 2017, FDA and EPA jointly issued final advice regarding fish consumption. This advice is geared toward helping women who are pregnant or may become pregnant – as well as breastfeeding mothers and parents of young children – make informed choices when it comes to fish that are healthy and safe to eat. (The advice refers to fish and shellfish collectively as “fish.”)

To help these consumers more easily understand the types of fish to select, the agencies have created an easy-to-use reference chart that sorts 62 types of fish into three categories:

- “Best choices” (eat two to three servings a week)
- “Good choices” (eat one serving a week)
- “Fish to avoid”

Fish in the “best choices” category make up nearly 90 percent of fish eaten in the United States.

An FDA analysis of fish consumption data found that 50 percent of pregnant women surveyed ate fewer than 2 ounces a week, far less than the amount recommended. Because the nutritional benefits of eating fish are important for growth and development during pregnancy and early childhood, the agencies are advising and promoting a minimum level of fish consumption for these groups. The advice recommends 2-3 servings of lower-mercury fish per week, or 8 to 12 ounces. However, all fish contain at least traces of mercury, which can be harmful to the brain and nervous system if a person is exposed to too much of it over time. The maximum level of consumption recommended in the final advice is consistent with the previous recommended level of 12 ounces per week. The new advice is consistent with the 2015 - 2020 Dietary Guidelines for Americans.

When updating the advice, the agencies took a cautious and highly protective approach to allow consumers to enjoy the benefits of fish while avoiding those with higher levels of mercury, which is especially important during pregnancy and early childhood. The average mercury content of each type of fish was calculated based on FDA data and information from other sources. The updated advice cautions parents of young children and certain women to avoid seven types of fish that typically have higher mercury levels: tilefish from the Gulf of Mexico; shark; swordfish; orange roughy; bigeye tuna; marlin; and king mackerel.

For fish caught recreationally, consumers are urged to check for local advisories where they are fishing and gauge their fish consumption based on any local and state advisories for those waters. If no information on fishing advisories is available, eat just one fish meal a week from local waters and also, avoid other fish that week. Consumers should clean and trim the fish they catch

of fat and skin, since locally-caught fish may contain contaminants besides mercury that can be reduced by proper trimming and cooking, (e.g. broiling instead of frying can reduce some contaminants by letting fat drip away from the fish).

All retailers, grocers and others are urged to post this new advice, including the reference chart listing fish to choose, prominently in their stores so consumers can make informed decisions when and where they purchase fish. The agencies will be implementing a consumer education campaign working with a wide array of public and private partners featuring the new advice.

39. Shrimp Imports

The Committee is concerned the FDA continues to detect an alarming amount of imported shrimp raised with hormones, antibiotics, or other drugs not approved for use in the United States. Therefore, the Committee directs the FDA to work with Customs and Border Protection [CBP] to establish a 2-year pilot program to better track shrimp imports and inspections by port of entry, in order to increase enforcement and improve food safety. In addition, the Committee directs the FDA to assist CBP to provide details on opportunities for enhancing FDA and CBP coordination on improving the safety of shrimp imports into the U.S., initial, both for a briefing required of CBP within 180 days and for the overall pilot program report.

FDA Response:

FDA has a variety of tools to help monitor and determine compliance with seafood safety requirements and has the ability to track import information, import activities, and inspections related to products, including shrimp, offered for import into the U.S. through existing data systems, some of which are directly linked to CBP data systems. FDA screens all import entries electronically prior to a product entering U.S. commerce. As part of the Agency's surveillance activities at the border, a subset of those entries are physically examined by FDA investigators and may subsequently be sampled and analyzed depending on the potential risk associated with each shipment. If deficiencies are found with a product offered for import, the Agency can issue an Import Alert. Additionally, FDA may conduct sampling of an imported product during the course of a domestic inspection.

FDA also conducts inspections of foreign processing facilities for compliance with FDA regulations and requirements including those concerning seafood HACCP. During an inspection, FDA investigators may also follow up on previous issues of concern or other information that the Agency has obtained through a variety of means, including data entered on commodities offered for import into the U.S.

FDA already utilizes data to coordinate Agency surveillance and enforcement activities and identify trends that may be occurring in the imported shrimp industry. To help prevent adulterated fishery products from entering domestic commerce, FDA has a monitoring program that also includes testing for residues of unapproved antibiotic chemicals and drugs. Upon discovering any use of an unapproved drug through the testing program or evidence developed during an FDA foreign inspection, FDA typically employs several tools, including Import Alerts, communication to the foreign government's competent authority, increased surveillance by FDA of the potentially adulterated products, and other actions such as seizure.

In addition, it is important to note that FDA is already working closely with CBP on imported seafood activities through mutual involvement with the Presidential Task Force on Combating Illegal, Unreported, and Unregulated (IUU) Fishing and Seafood Fraud. These activities are coordinated, in part, through FDA's presence at the Commercial Targeting and Analysis Center (CTAC) as well as interaction at ports of entry. Based on an IUU recommendation, there already is a pilot program regarding seafood fraud, and imported shrimp is a major commodity to be targeted.

In light of these activities already underway, we do not feel there is a need for an additional pilot program as described in the report language at this time, but would be happy to further discuss this with the Committee.

40. Sodium Guidance

The Committee is aware that the FDA is considering issuing guidance to food manufacturers in order to reduce sodium in various food categories. It is imperative that any guidance be issued using the latest sound science. The Centers for Disease Control and Prevention and the IOM are working together to update the Dietary Reference Intake [DRI] report on sodium. The FDA is encouraged to issue any voluntary or mandatory guidance based upon an updated DRI report.

FDA Response:

In June 2016, FDA issued draft guidance for public comment for voluntary sodium reduction goals in commercially processed and prepared food, both in the short-term and over the long-term (81 FR 35363). This draft guidance was based on the latest scientific evidence available, and reflects recommendations in the most recent Dietary Reference Intakes (DRI)¹⁰⁷ for sodium, as well as the recently issued 2015-2020 *Dietary Guidelines for Americans* (which involved expert review of the current body of research by the Dietary Guidelines Advisory Committee). FDA's draft voluntary short-term (two-year) targets are aimed at reducing average sodium consumption from 3,400 to 3,000 mg/day, and the voluntary long-term (ten-year) targets are aimed at reducing average sodium consumption to 2,300 mg/day, which is consistent with current federal recommendations. FDA also strongly supports efforts by the National Academies of Science, Engineering and Medicine (National Academies) to formally review the sodium DRI, and FDA is collaborating with CDC, NIH, and USDA to update the DRI for sodium as expeditiously as possible.

The majority of Americans are trying to take action to reduce their sodium (CDC, 2015), and the weight of the scientific evidence supports reducing sodium in the food supply in order to reduce current average sodium consumption levels from 3,400 mg/day—well above the current recommended limit of 2,300 mg/day—thereby reducing the risks associated with increased blood pressure and cardiovascular disease (CVD). Three quarters of sodium intake comes from processed or prepared food – before it is added at the table, or during cooking. Supporting options for food products lower in sodium therefore increases choices for American consumers. Several major food manufacturers are supportive of FDA's efforts in their recently submitted comments on the draft voluntary sodium reduction targets.

¹⁰⁷ The Dietary Reference Intakes (DRIs) are nutrient reference values developed by the Institute of Medicine of The National Academies of Sciences, Engineering, and Medicine.

Given the scientific evidence in support of reducing sodium intake from current levels to reduce blood pressure, subsequent CVD, and associated health care costs, as well as recent industry feedback on the targets, the Agency believes that it is reasonable to continue work on voluntary sodium reduction targets, even as the DRI is updated. Once the DRI report is finalized (anticipated to be in 2019), FDA is committed to making any needed adjustments to the long-term targets to align them with the findings of the National Academies Committee. Furthermore, FDA will continue extensive outreach with industry and public health groups on our draft voluntary targets to ensure that they are well understood.

41. Sunscreen Ingredients

The Committee is significantly concerned that despite the increase in incidence of skin cancer in the United States, and the January 2016 Presidential Memorandum creating the White House Cancer Moonshot Task Force to prevent and cure cancer, FDA has still not approved a new over-the-counter sunscreen ingredient through the process created by the Sunscreen Innovation Act [SIA]. The Committee has, for multiple years, directed the FDA to clear the sunscreen backlog, and the agency has failed to do so. Therefore, the Committee directs the FDA to include in its report to Congress required by section 4(c) of the SIA by May 26, 2016, an update on how the agency plans to work with stakeholders to resolve the science-based concerns raised in public comments and describe how the agency is appropriately balancing the benefit of additional skin cancer prevention tools versus the hypothetical risk of OTC sunscreens that have been used around the world for decades. FDA is further directed to work with stakeholders to come to an agreement on an appropriate, science-based testing regimen by June 20, 2016. The Committee recommendation maintains the funding increase provided in fiscal year 2016 to address this public health threat. In addition, the Committee directs the FDA to finalize a rule limiting the maximum Sun Protection Factor [SPF] to “50” or “50 δ ”, which was first proposed in 2011, within 90 days of enactment of this Act, and to issue a proposed rule to establish testing and labeling standards for sunscreen sprays within 90 days of enactment of this act.

FDA Response:

FDA transmitted the report entitled “Report to the Committee on Appropriations: Sunscreen Ingredients” to the committee on May 16th, 2016.

FDA has carefully considered what information is needed to ensure that a particular sunscreen active ingredient is safe and effective for use in OTC sunscreen products. FDA’s recommended studies reflect the Agency’s scientific expertise, existing technical guidance, experience from reviewing safety and efficacy data submitted for a generally recognized as safe and effective (GRASE) review of sunscreen active ingredients seeking to be added to the OTC Review for Sunscreens under current OTC drug regulations, and input from outside scientific experts (<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm407137.htm>). The recommended studies are not novel and are consistent with FDA’s standard data requirements for both nonprescription and prescription topical drugs intended for chronic use.

Information on FDA’s recommendations and expectations for the safety data needed to show that an active ingredient is GRASE for use in nonprescription sunscreen products has been publicly

shared with industry and other interested parties on multiple occasions, including a public advisory committee meeting held in September 2014, proposed sunscreen orders published in 2014 and early 2015 for the eight sunscreen active ingredients that were under evaluation by FDA when the SIA was enacted, sponsor-requested meetings on the proposed sunscreen orders, and an SIA-required draft guidance for industry published in November 2015 which the FDA finalized in November, 2016.

To date FDA has met all statutorily mandated SIA deadlines and remains committed to achieving that goal in the future. As required by the SIA, the FDA is working to finalize OTC monograph regulations for sunscreens by November 26, 2019. The agency anticipates including provisions related to the effectiveness of various SPF levels and dosage forms for sunscreens. The FDA also intends to publish a proposed rulemaking on sunscreens prior to this date in order to provide the opportunity for public comment.

42. Vibrio

The Committee is aware of the public health challenge related to the naturally occurring bacteria called *Vibrio parahaemolyticus* that can accumulate in shellfish and believes that more scientific research is necessary to develop proper controls that will reduce the risk to consumers and sustain a healthy domestic shellfish industry. The Committee encourages the Food and Drug Administration [FDA] to increase funding for research into *Vibrio* illnesses associated with the consumption of raw molluscan shellfish, improve risk assessment models, and develop improved rapid detection methods for virulent *Vibrio* strains.

FDA Response:

FDA shares your concern regarding the public health challenge posed by *Vibrio parahaemolyticus* in shellfish. We are aware of, and actively engaged in activities aimed at reducing the risk that *Vibrio parahaemolyticus* (V.p.) poses to consumers of raw oysters and clams. FDA actively participates with federal, state and industry partners in the Interstate Shellfish Sanitation Conference (ISSC), which plays a key role in the development of the National Shellfish Sanitation Program (NSSP) Model Ordinance. The NSSP contains the standards and controls for implementation by state health authorities and the shellfish industry for controlling the safety of raw molluscan shellfish. FDA works directly with the ISSC *Vibrio* Management Committee and the CDC to examine the incidence of V.p. illness and to engage the ISSC to adopt improved controls into the NSSP.

FDA has participated in a number of other collaborative efforts with state health authorities and the shellfish industry. For example, FDA works with state shellfish industry members to develop and implement shipboard controls to reduce risk through rapid onboard cooling techniques. Through this effort, FDA has seen a number of industry members implement controls that exceed those currently established in the NSSP and which have achieved significant additional illness reduction.

With respect to research funding, FDA has awarded the ISSC grants aimed at helping to ensure that, in the U.S., the safety net for molluscan shellfish is consistently and uniformly managed at the state and industry level with administrative oversight from FDA, as well as ISSC efforts to examine the science of V.p. and develop control measures aimed at reducing the risk of V.p.

FDA also has awarded additional funding to the ISSC to support independent studies conducted by state shellfish authorities, including studies by three states (WA, NJ, CT) aimed at defining science-based industry practices to reduce the risk of V.p. in raw molluscan shellfish. In further support of this effort, FDA again awarded funding to the ISSC in 2015 to support continued research intended to enhance our understanding of V.p. and how current and innovative industry practices impact and may reduce risk.

FDA has also established a Workgroup on Ecological Forecasting for Vibrio. The goal for establishing the workgroup is to coordinate, plan, prioritize, and communicate ecological forecasting activities related to Vibrio within and beyond FDA. Specifically, FDA has collaborated with NOAA under their Ecological Forecasting Roadmap to develop experimental Vibrio forecast products (among others) using FDA's risk models and NOAA's environmental data and hydrodynamic models.

Additionally, FDA has offered a program to extend research and technical assistance on Vibrio to states and industry through the Vibrio Assessment Review Board (VARB). States and industry submit to FDA's VARB requests for research and technical assistance aimed at improving the science and control of Vibrio in molluscan shellfish. Through the VARB, FDA offers, as resources allow, assistance such as laboratory support, technical expertise, and statistical application to aid states and industry as they undertake independent Vibrio projects.

43. White Oak Expansion

The Committee is aware of the need for FDA facilities to accommodate an anticipated expanded workforce due to broader missions related to food safety and other mandates in legislation over the last few years. Due to the challenging fiscal environment, the Committee encourages the FDA and GSA to consider innovative financing options to allow for the space allocation required. In particular, the Committee directs the FDA and GSA to consider partnership opportunities with non-Federal Government entities that provide reasonable cost options that will enable the FDA to maintain very close proximity to its campus headquarters in White Oak, including space contiguous to the White Oak campus.

FDA Response:

FDA appreciates the recognition of its expanding mission and workforce, the challenging fiscal environment that currently prevents expansion on the White Oak Campus, and the importance of housing FDA staff that exceed the current capacity of the White Oak Campus in very close proximity to the Campus. In FY 2017, FDA began working with GSA to develop a housing strategy to establish the housing demand for staff and continue geographically consolidating FDA's headquarters activities. In Q4 FY 2017, a GSA housing strategy deliverable will establish the requirements for campus-proximate space. GSA will use these requirements to determine the methods to fulfill FDA's space needs. GSA has been in contact with non-Federal Government entities that have indicated they can provide options that will enable FDA to expand into space contiguous with the White Oak Campus. FDA has met with GSA and the aforementioned entities, and is open to potential opportunities that allow for critically needed office space to accommodate FDA's expanding workforce that will further FDA's geographic consolidation.